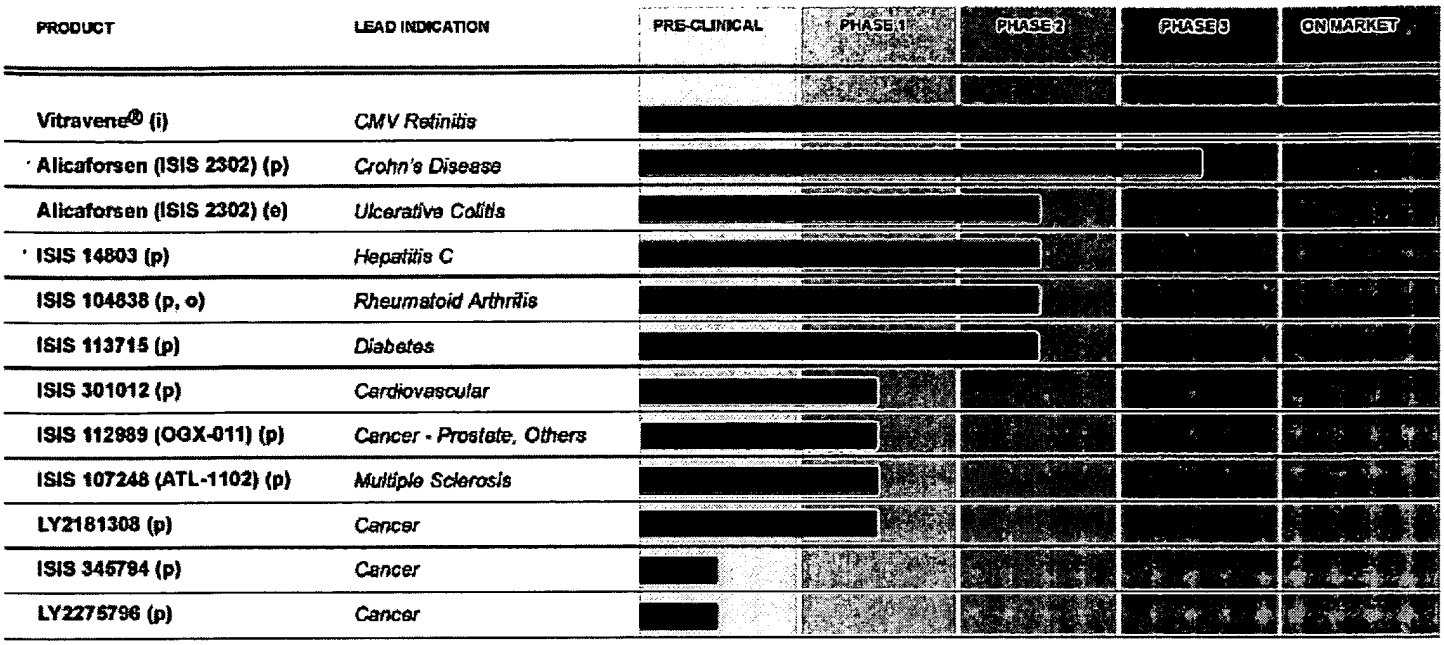
ISIS PIPELINE AT-A-GLANCE



i = INTRAVITREAL
p = PARENTERAL
e = ENEMA
o = ORAL

Alicaforsen (ISIS 2302) is a first-generation enema formulation that has recently completed positive Phase 2 clinical trials in patients with ulcerative colitis. Isis plans to move forward with this drug and initiate Phase 3 trials.

Ulcerative Colitis (UC):

Isis is conducting two Phase II clinical trials of alicaforsen in patients with UC. The purpose of the first study is to compare the safety and efficacy of an enema formulation of alicaforsen to mesalamine enema, a widely used medication for UC. Approximately 170 patients have been enrolled in the randomized, double-masked, active-controlled Phase II study at multiple sites in the U.S.

A second trial is examining the safety and efficacy of different regimens of alicaforsen enema (for example, daily administration compared to treatment every other day) versus placebo for six weeks. Approximately 100 patients have been enrolled at multiple sites throughout the U.S. and Europe.**(UC clinical trials)**

Isis initiated these Phase II studies following the outcome of an initial placebo-controlled, double-blinded European Phase II clinical trial (reported in October 2001). Results from the trial demonstrated that UC patients treated with alicaforsen experienced a dose-dependent reduction in disease activity index score (DAI) and clinical activity index score (CAI), common clinical index scoring systems of the severity of symptoms related to UC. More importantly, the study showed considerable durability of the beneficial response. Alicaforsen and method of administration were well tolerated by patients. **(press release)**

In addition, Isis reported results of a Phase II study of alicaforsen in pouchitis patients at the American College of Gastroenterology (ACG) in 2003. Pouchitis is a UC related condition. The primary endpoint of the trial was improvement in the Pouchitis Disease Activity Index (PDAI), a commonly used 18-point system that evaluates patients' symptom score, endoscopy and histology (each category is scored on a 0-6 scale).

Results from the 12 patients having up to nine months of follow-up are:

• Patients showed improvement in their disease as measured by PDAI and clinical PDAI
- Mean PDAI for all patients in the study decreased from a baseline value of 11.4 to 6.8 after six weeks of treatment. Remission is traditionally defined by a value less than 7. This result was statistically significant (p=0.001).
- Clinical benefit was also observed when evaluating the clinical PDAI (clinical symptom score and endoscopy). Mean clinical PDAI score decreased rapidly from a baseline value of 9.0 to 4.4 (p=0.002) at 6 weeks and was maintained through week 10.

• The most significant improvement was measured by endoscopic analysis of inflamed tissue. Patients experienced a significant improvement in mean endoscopic scores after 6 weeks of treatment (from baseline value of 5.3 to 2.6, p=0.0005) with sustained improvement of up to nine months.

• Alicaforsen enema was well tolerated. **(press release)**

ICAM-1: The Target

Alicaforsen is an antisense inhibitor of ICAM-1, a molecule that plays a key role in a wide range of inflammatory and autoimmune conditions such as Crohn's disease and ulcerative colitis. It is involved in the recruitment and activation of immune cells associated with the inflammatory response in these diseases. ICAM-1 is part of a molecular family (known as Cellular Adhesion Molecules, or CAMs) that can be found on the surface of virtually every cell in the body, including cells that line the inflamed gastrointestinal (GI) tract.

Inflammatory Bowel Diseases (IBD) Facts

According to the Crohn's and Colitis Foundation of America (CCFA) up to one million people have inflammatory bowel disease, evenly split between Crohn's disease and UC. According to the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) a similar number of people in Europe are affected. **(return to pipeline chart)**

ISIS 14803 is being evaluated in patients with drug-resistant chronic hepatitis C virus (HCV). In June 2002, Isis announced the initiation of a Phase II study to assess the benefit of adding ISIS 14803, an antisense inhibitor of HCV viral replication, to standard treatments for hepatitis C virus (HCV). In this trial, ISIS 14803 will be administered to patients who do not achieve an early response to treatment with pegylated interferon and ribavirin.

The company plans to enroll approximately 30 people with genotype 1, drug-resistant HCV in the open-label, dose-escalation study. Along with conventional doses of pegylated interferon and ribavirin, patients will receive ISIS 14803 twice weekly for three months and be followed to determine whether sustained viral responses are achieved. The trial will also assess treatment safety.

ISIS 14803 demonstrated promising antiviral activity by producing up to 3.8 log dose-dependent reductions in plasma virus levels in patients with HCV, according to final results of a Phase II study reported in October 2003. The majority of the 43 patients participating in the three-month study were HCV genotype 1, the most common and difficult to treat form of HCV, and all but four had been previously treated with interferon.

Two doses and two treatment schedules of ISIS 14803 were evaluated in this trial. All patients initially received 2.5 mg/kg of ISIS 14803 three times a week for two weeks. Patients then received 4 mg/kg or 6 mg/kg of ISIS 14803 either once weekly or twice weekly for 10 weeks by intravenous infusion.

Data highlights are as follows:

-- Five of 17 patients receiving 6 mg/kg of ISIS 14803 twice a week experienced viral titer reductions of 1.0 - 3.8 logs; three patients experienced a greater than 3.0 log reduction.

-- Based on these data, a dose of 6 mg/kg twice weekly will be studied in further clinical trials.
-- In the trial, decreases in viral titers were accompanied by asymptomatic transient increases in alanine aminotransferase (ALT) levels. These data suggest that ALT elevations may correlate with antiviral activity of ISIS 14803.

In an initial one-month Phase I/II study of the antisense drug in patients with chronic hepatitis C virus, escalating doses of ISIS 14803, administered three times a week for one-month by either intravenous infusion or subcutaneous injection, were evaluated. In the trial, five of 28 patients had meaningful viral reductions. Three of 10 patients that received 2 mg/kg of ISIS 14803 experienced 1.3-2.2 log reductions in viral levels. Reductions in viral titers were maintained for more than 40 days. ISIS 14803 was well tolerated in the Phase I/II clinical trial. Adverse events reported were minor. **(press release)**

IRES: The Target
ISIS 14803 targets the IRES/translation region of the hepatitis C virus inducing degradation of the viral RNA and inhibits the translation of viral proteins. These effects have the potential to reduce or halt HCV production.

HCV Facts:
HCV represents a major public health challenge. This potentially deadly disease affects the liver and can eventually cause liver cirrhosis and death. It is estimated that nearly four million people in the United States are infected with HCV. Ten thousand to 12,000 people in the United States are expected to die from this disease each year. There are at least six major genotypes and more than 50 subtypes of HCV. Genotype 1 is the most common genotype in the United States. **(return to pipeline chart)**

ISIS 104838 is being studied in patients with rheumatoid arthritis (RA). It is the first drug based on Isis' proprietary **second-generation chemistry**, called 2'-*O*-methoxyethyl, to enter clinical trials.

Results from Phase I safety studies of intravenous (I.V.) and subcutaneous (S.Q.) delivery of ISIS 104838 demonstrated that antisense drugs based on this improved chemistry offer patients a more convenient dosing schedule, as well as safety advantages. The study also demonstrated substantial improvement in potency and local tolerability compared to first-generation antisense drugs.

Rheumatoid Arthritis

As announced in January 2004, ISIS 104838 produced a significant disease response in patients with rheumatoid arthritis (RA). In the randomized, placebo-controlled trial, 157 evaluable RA patients received subcutaneous injections of either placebo or one of three dose regimens of 200 mg of ISIS 104838: every other week, once weekly or twice weekly. Patients receiving the once- and twice- weekly doses experienced similar responses to treatment, with 41% of evaluable patients achieving a 20% decrease in disease activity. In comparison, 23% of placebo-treated patients achieved a 20% decrease ($p=0.05$). Response to ISIS 104838 treatment was measured by the American College of Rheumatology (ACR 20) response criteria, a widely used index of RA severity. **(press release)**

These Phase II results add to Isis' strong portfolio of data demonstrating activity of ISIS 104838. Another component of this data package is the Phase II biomarker study which evaluated the biological effect of TNF-alpha inhibition by ISIS 104838 in 20 RA patients over a four-week treatment period. As reported in 2003, ISIS 104838 accumulated in synovial tissue in a dose-dependent manner, reducing TNF-alpha mRNA levels in patients with RA who received 300 mg of the second-generation antisense drug. The synovium, the lining surrounding joints, is inflamed in patients with RA. **(press release)**

Oral Formulations Program

The company is accelerating development of the oral formulation of ISIS 104838 for the treatment of RA. Isis plans to initiate a Phase 2 trial comparing the oral and subcutaneous formulations of ISIS 104838 in patients with RA. In the planned study, which will be conducted outside the U.S., ISIS 104838 will be dosed in combination with methotrexate, a commonly used treatment for RA. Isis expects to initiate this trial in mid-2005.

In November 2002, Isis announced seminal results from a Phase I study in healthy volunteers demonstrating for the first time that solid doses of antisense drugs can be delivered orally. A proprietary capsule formulation of ISIS 104838 achieved drug plasma concentrations sufficient to support further clinical development. Additional Phase I trials will further refine the formulation. Based on these data, Isis will select a lead oral formulation and dose schedule that it will further optimize and advance into Phase II clinical trials. **(press release)**

TNF-alpha: The Target

ISIS 104838's target, TNF-alpha, is a naturally occurring cytokine that is an immune system protein responsible for contributing to the activity and progression of many inflammatory diseases. High blood concentrations of TNF-alpha have been observed in patients with RA, Crohn's disease, multiple sclerosis, sarcoidosis, acute liver failure, transplant rejection, congestive heart failure, rheumatoid arthritis and various skin conditions, including psoriasis.

In RA, TNF-alpha is known to be a major mediator of joint pathology as it stimulates bone and cartilage resorption and drives inflammation. In psoriasis, TNF-alpha contributes to the activity of both skin disease and psoriatic arthritis. In Crohn's disease, TNF-alpha inhibition has been shown to close fistula and decrease disease activity.

RA Facts:
According to the Arthritis Foundation, RA affects 2.1 million Americans, predominately women. RA is a systemic disease that affects the entire body and is one of the most common forms of arthritis. RA is characterized by the inflammation of the membrane lining in the joint, or synovium, which causes pain, stiffness, warmth, redness and swelling. The synovium can invade locally and causes damage to bone and cartilage. Inflammatory cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement.

OGX-011 (ISIS 112989) is an anti-cancer antisense drug, which inhibits clusterin. OGX-011 is currently in Phase I/II development for patients with prostate cancer and other solid tumors.

OncoGenex Technologies, Inc, based in Canada, announced results in June 2004 of a study evaluating OGX-011 as a single agent in patients with high-risk prostate cancer. The Phase I study showed that once weekly intravenous administration of OGX-011 is well tolerated, achieves excellent drug concentration in target tissue, and produces a 91 percent dose-dependent down-regulation of its target, clusterin, in prostate cancer. In the Phase I dose escalation trial, which was coordinated by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), investigators reported significant, dose-dependent inhibition of clusterin in prostate cancer patients compared to historical controls at several of the doses studied:

- 91 percent target reduction with a 640 mg dose of OGX-011
- 73 percent target reduction with a 480 mg dose of OGX-011
- 66 percent target reduction with a 320 mg dose of OGX-011
- 58 percent target reduction with a 160 mg dose of OGX-011

OGX-011 was well tolerated at the doses studied. The most frequently reported side effects were mild (grade 1 or 2) and included fevers, rigors, fatigue and transient elevations of AST and ALT, enzymes used to detect liver damage. No dose limiting toxicities were observed in the trial.

Based on tissue pharmacokinetic and optimal inhibition of the drug's target in prostate cancer cells and lymph nodes, 640 mg was recommended as the optimal dose for future Phase II studies of OGX-011. Trials of OGX-011 in

combination with hormone and chemotherapy are planned to begin in 2004 in patients with prostate, breast and lung cancers.

A second Phase I study is in progress which is designed to determine recommended dose of OGX-011 in combination with TAXOTERE® in various solid tumors. This study is expected to be completed by the end of Q3, 2004. **(press release)**

OncoGenex and Isis established a drug development collaboration in 2001 to develop and commercialize OGX-011. This partnership combines OncoGenex's proprietary antisense position in secretory protein clusterin (sCLU) inhibitors with Isis' proprietary second-generation antisense chemistry called 2'-*O*-methoxyethyl. **(press release)**

Secretory Protein Clusterin (sCLU): The Target
OGX-011 is an inhibitor of sCLU, which is in the clusterin (CLU) family of proteins. sCLU acts as a cell-survival protein and is over-expressed in response to tumor killing strategies, such as chemotherapy, hormone ablation and radiation therapy. sCLU has been associated in preventing cell death in tumors, a function that may be related to its ability to clear cell debris after damage from tumor killing strategies. Inhibiting sCLU is intended to enhance the effects of traditional therapies in cancer treatment.

Prostate Cancer Facts:
According to the American Cancer Society, an estimated 230,110 new cases of prostate cancer will be diagnosed in the U.S. during 2004. An estimated 29,900 deaths from prostate cancer will occur this year, making the disease the second leading cause of cancer death in men. **(return to pipeline chart)**

ISIS 113715 is a second-generation antisense drug in Phase II development for the treatment of type 2 diabetes. The drug is currently in Phase II development with the goal of evaluating the drug's ability to regulate blood sugar levels in patients with type 2 diabetes.

Phase 2 development was initiated based on robust Phase I and preclinical data. In a Phase I study, ISIS 113715 enhanced insulin's ability to transport glucose, or blood sugar, into cells in normal volunteers. A primary characteristic of type 2 diabetes is inefficient use of glucose in spite of the availability of insulin. Correcting this defect is a goal in the management of the disease. ISIS 113715 did not cause hypoglycemia, or excessively low blood sugar, which is an adverse effect observed with many currently available treatments for type 2 diabetes. ISIS 113715 was well tolerated in the Phase I study.

In preclinical studies, ISIS 113715 demonstrated positive effects in five well-characterized and accepted animal models of diabetes. The drug normalized blood sugar levels in multiple rodent models and improved glucose tolerance in normal and obese monkeys. In addition, ISIS 113715 did not produce hypoglycemia or weight gain, a characteristic of many other type 2 diabetes treatments. ISIS 113715 has demonstrated consistent reduction of PTP-1B mRNA and protein levels in liver and fat, key tissues known to be important in the regulation of blood sugar levels.

PTP-1B: The Target
Diabetic patients are often prescribed insulin injections in order to regulate blood sugar. Insulin is a hormone secreted by the pancreas that directs cells to uptake sugar from the blood stream, thereby decreasing sugar concentration in the blood stream. PTP-1B is an enzyme that appears to reduce insulin's ability to regulate blood sugar levels. The inhibition of PTP-1B may allow the insulin receptors to stay active longer, allowing for more glucose uptake into cells and lowers levels in the blood stream.

Type 2 diabetes patients produce insulin, but their bodies do not react to the insulin, hence glucose is not absorbed into their cells and it is left in the blood stream. Over time, patients may become desensitized to insulin and will then require higher doses of insulin. The successful inhibition of PTP-1B may allow for the administration of lower doses of

insulin to diabetic patients while still maintaining satisfactory blood sugar levels. **(press release)**

Type 2 Diabetes Facts:
According to the National Institutes of Diabetes and Digestive and Kidney Diseases, more than 17 million Americans are affected by diabetes, a metabolic condition that affects the body's use of sugars. Type 2 diabetes, also known as adult-onset diabetes, accounts for 90-95% of all diagnosed diabetes cases. **(return to pipeline chart)**

ATL 1102 (ISIS 107248) is a second-generation antisense inhibitor of VLA-4, which is in development for multiple sclerosis (MS). Inhibition of VLA-4 has been shown to have positive effects in multiple animal models of inflammatory diseases, including MS.

Results of a dose-escalating Phase 1 study of ATL-1102 announced in June 2004 showed that 6 mg/kg/week of ATL-1102 appeared well-tolerated and has been selected as the proposed dose for Phase 2 development. A Phase 2 clinical trial is expected to begin in the second half of 2004.

The double-blind, randomized, dose-escalation, placebo-controlled Phase 1 study evaluated the pharmacokinetic and safety profile of ATL-1102. In 54 healthy volunteers, ATL-1102 was either delivered in an intravenous (IV) or subcutaneous (SQ) formulation. ATL-1102 was well-tolerated. The most frequently reported side effects included mild "flu-like" symptoms and occasional injection site reactions, which were generally mild and increased in incidence and severity with escalating dose levels, particularly at 12 and 18 mg/kg/week. The trial was conducted at the Charterhouse Clinical Research Unit of the Ravenscourt Park Hospital (formerly Stamford Hospital) in London. **(press release)**

Isis licensed ATL-1102 to Australian-based Antisense Therapeutics Limited (ATL) in 2001. Isis completed preclinical studies, and ATL is responsible for future clinical development, manufacturing and commercialization of the compound.

VLA-4: The Target

ATL-1102 is an inhibitor of CD 49d, a sub-unit of VLA-4 (Very Late Antigen-4). In multiple sclerosis, white blood cells (leukocytes) are pulled into the central nervous system (CNS) from the blood. The inhibition of VLA-4 may prevent white blood cells from entering the CNS to stop the progression of MS. Inhibition of VLA-4 in animals has demonstrated positive effects in a number of inflammatory diseases such as MS.

Multiple Sclerosis Facts

According to the National Multiple Sclerosis Society, approximately one third of a million Americans acknowledge having MS and every week about 200 people are diagnosed. Worldwide, MS may affect 2 million individuals. **(return to pipeline chart)**

LY 2181308(ISIS 23722) is a second-generation antisense drug was licensed to Eli Lilly and Company as a component of the companies antisense cancer drug discovery collaboration initiated in 2002. The oncology relationship builds on a broad, ongoing strategic alliance established to discover antisense drugs in the areas of inflamatory and metabolic diseases. **(press release)**

In April 2003, Isis achieved a significant milestone in the development of LY2181308. In preclinical studies, LY2181308 demonstrated activity in multiple *in vivo* models of cancer. In November 2004, Lilly initiated Phase 1 clinical trials in cancer patients.**(press release)**

Survivin: The Target

LY2181308 targets survivin, a molecule that allows the survival of cells that would normally undergo programmed cell death or apoptosis. When cancer cells grow, they appear to need the help of survivin. The molecule is abundant in many types of cancers, including colon, brain, lung, skin and others, but nearly nonexistent in normal cells. **(return to pipeline chart)**

ISIS 301012 is a second-generation drug that targets ApoB-100, which is a protein that plays a pivotal role in the production of low-density lipoprotein (LDL), the "bad" cholesterol.This molecule has been of great interest to the industry, yet has long been considered "undruggable" by traditional small molecule approaches.

The company initiated a Phase I study in late 2003. The double-blind, placebo-controlled, dose-escalation trial will enroll 40 healthy volunteers with borderline cholesterol. The goal of this trial is to assess the safety, tolerability and pharmacokinetic profile of ISIS 301012, and its ability to reduce several components of cholesterol that are important in the management and prevention of cardiovascular disease.

The company reported preliminary results of this Phase I study in August 2004 on the first 19 volunteers.

Preliminary Study Highlights:

* At Day 25, volunteers in the top three ISIS 301012 dose groups of 100 mg, 200 mg and 400 mg per dose demonstrated average decreases in lipids from baseline as follows:

* LDL reductions ranging from 27% (100 mg) to 44% (400 mg).
* VLDL reductions ranging from 14% (100 mg) to 38% (400 mg).
* Total cholesterol reductions ranging from 7% (100 mg) to 36% (400 mg).

* In addition, initial data from the three highest dose groups showed:

* Volunteers receiving ISIS 301012 experienced average reductions from baseline in apoB-100 protein levels in serum of up to 55%.
* ISIS 301012's onset of action was rapid, with reductions in apoB-100 and lipids observed at the first treatment evaluation time point of one week.
* Reductions in apoB-100 and associated decreases in LDL, VLDL and total cholesterol remained below baseline for two months or longer in a majority of volunteers. In contrast, placebo-treated volunteers demonstrated negligible apoB-100 or lipid changes during the study.
* ISIS 301012 improved cholesterol/high density lipid (HDL) and LDL/HDL ratios.
* To date, no treatment-related serious adverse events have been reported :
* The most commonly reported side effect was skin reactions at the site of subcutaneous injections, which did not interfere with continued treatment and were comparable in frequency and similar in degree to skin reactions observed with other subcutaneously administered drugs.
* In addition, minor increases in liver enzymes were observed in some volunteers. The increases correlated with reductions in cholesterol, were asymptomatic and similar in degree to those observed with other lipid regulating agents. **(press release)**

Isis plans to expeditiously advance the development of ISIS 301012.

Cardiovascular Disease Facts

Cardiovascular disease is the leading cause of death in the U.S., according to the National Institutes of Health. Researchers have shown a strong correlation between high cholesterol levels and subsequent cardiovascular diseases. Statistics from the American Heart Association state that nearly 105 million American adults have borderline high cholesterol and about 37 million American adults have levels of 240 or above.

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ISIS 345794 is the latest compound to emerge from Isis' cancer research program. This second-generation antisense drug targets Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. In preclinical studies, antisense inhibition of STAT-3 significantly delayed tumor growth and increased the rate of cancer cell death in multiple cell and animal models of cancer. Isis plans to rapidly move ISIS 345794 into clinical development and anticipates initiating clinical trials in patients with cancer in 2005. **(press release)**

STAT-3: The Target

STAT-3 is a member of a multi-gene family called Signal Transducers and Activators of Transcription, which is involved in the regulation of cell growth. STAT-3 appears to play an important role in cell development and death, and is active in a wide range of cancers, including both solid and hematological cancers. Activated STAT-3 is present in numerous malignancies including head, neck, prostate, breast and lung cancers, and in multiple myeloma, anaplastic lymphoma, chronic myeloid leukemia and melanoma. The control of both the activation and inactivation of STAT-3 is equally important to maintain normal cell growth.**(return to pipeline chart)**

LY2275796 is the second anti-cancer drug candidate to be licensed to Lilly for clinical development. This second-generation antisense drug targets eukaryotic initiation factor- 4E (eIF-4E), a protein involved in the translation of key growth and survival factors that drive tumor progression, angiogenesis and metastases.

Lilly will fund the continued development of LY2275796 and under the terms of the companies' alliance, Lilly will pay Isis development and regulatory milestones and royalties on potential product sales. The Isis-Lilly oncology relationship, initiated in June 2002 and extended in 2004, builds on an ongoing alliance previously established by the companies to discover antisense drugs in the areas of inflammatory and metabolic diseases. **(press release)**

eIF-4E: The Target

LY2275796 targets eIF-4E, a protein that is upregulated or overexpressed in a variety of cancers, including breast, head and neck, prostate, lung, bladder, colon, thyroid and non-Hodgkin's lymphomas. The molecule facilitates the synthesis of tumor angiogenic factors (factors that facilitate the growth of new blood vessels to support the development and progression of tumors), growth factors and survival factors by selectively enhancing their translation. Based on scientific literature, there is a strong indication that eIF-4E may act as a critical "switch" in cancer progression.**(return to pipeline chart)**

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